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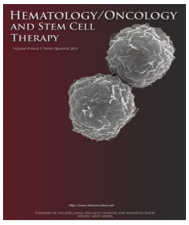

CASE REPORT

Polycythemia vera masked due to severe iron deficiency anemia

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Abstract
Polycythemia vera is one of the chronic myeloproliferative diseases and very few patients present with its actual clinical manifestations. The most common findings are increased red cell mass and an increased leukocyte count with decreased erythropoietin. We present a case where there was a delay in the diagnosis of polycythemia because of menorrhagia in the past. On admission, the patient presented with elevated red and white blood cell counts, erythropoietin was low, and polycythemia was then suspected. A bcr-abl test was performed to rule out chronic myelogenous leukemia. JAK2 mutation was positive, and the patient was diagnosed with polycythemia vera.

Introduction

Polycythemia vera (PV) is one of the chronic myeloproliferative disease characterized by increased red cell mass on normal hemoglobin oxygen saturation, and may have an elevated white cell count and an elevated platelet count. Low erythropoietin levels and JAK2 mutation are highly specific for PV. Here we present a case of a 52-year-old female who had a history of severe iron deficiency anemia due to menorrhagia from fibroids and was diagnosed with PV only after having amenorrhea for 8 months.

Case report

A 52-year-old African-American female presented to a hospital in March 2016 with shortness of breath and cough for 3–4 days. She also complained of Grade 3 dyspnea. She denied any history of pruritus, dizziness, vasomotor symptoms, fatigue, and paresthesia. Past medical history

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was significant for chronic obstructive lung disease, obesity, diabetes, and peptic ulcer disease. She had a history of anemia due to severe menorrhagia from fibroids. She has been amenorrheic for 8 months now and was placed on oral iron therapy twice a day for anemia. Her social history was positive for smoking with a 20 pack year index, but there was no history of alcohol or illicit drug use.

On physical examination the vital signs were stable; the left eye showed subconjunctival congestion. Chest, cardiovascular, abdominal, and neurological examinations were normal. Laboratory data on admission are given in Table 1.

The patient was suspected to have secondary polycythemia. Her arterial blood gas (ABG) showed the following: pH, 7.33 (7.35—7.45); pCO_2, 45 mmHg (30—44 mmHg); pO_2, 132 mmHg (90—108 mmHg); and FiO_2, 20%. However, her erythropoietin was 1 mU/mL (normal reference range for adults: 4—20 mU/mL).

On reviewing her past records from June 2011 to May 2015, her white blood cell (WBC) count was persistently on the higher side (ranging from 11.77×10^9/L to 38.13×10^9/L), platelets were intermittently high (334—649×10^9/L), and hemoglobin (Hb) level was intermittently on the lower side due to menorrhagia (ranging from 6.8 g/dL to 11.9 g/dL). She had consistent severe microcytic hypochromic anemia. In November 2013, her complete blood count parameters were as follows: Hb, 6.8 g/dL; mean corpuscular volume, 56.8 fL; mean corpuscular hemoglobin, 14.4 pg; and mean corpuscular hemoglobin concentration, 25.4 g/dL. Her iron studies revealed the following: iron, 8 μg/dL (normal: 28—170 μg/dL); total iron-binding capacity (TIBC), 426 μg/dL (normal: 269—535 μg/dL); transferrin, 304 mg/dL (normal: 192—382 mg/dL); transferrin saturation, 2% (normal: 15—60%); and ferritin, <1 ng/L (normal: 10—291 ng/mL).

On admission, the patient's lactate dehydrogenase (LDH) was 1112 U/L (normal range: 300—500 U/L). Abdominal ultrasound showed a spleen size of $16 \times 6 \times 6$ cm^3. Chronic myeloid leukemia was ruled out with negative bcr-abl. A JAK2V617F mutation test was ordered, which was found to be positive, and PV was diagnosed. In the hospital, her oral iron therapy was discontinued and a therapeutic phlebotomy was performed. She refused further phlebotomies and was started on hydroxyurea 1500 mg daily.

Table 1 Laboratory data revealed.

Complete blood count	Result	Reference range
Hemoglobin (g/dL)	20.6	11.5—16.0
Hematocrit (%)	64.6	32.0—45.0
RBC (M/μL)	7.6	4.00—5.506
Red cell width (%)	18.0	0—18.10
MCV (fL)	85.2	75.0—102.0
MCH (pg)	27.1	26.0—34.0
MCHC (g/dL)	31.9	30.5—36.0
WBC ($\times 10^9$/L)	27.8	3.40—11.00
Platelets	399×10^9/L	$130—400 \times 10^9$/L

Note. MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; WBC = white blood cell.

Discussion

The incidence of PV is 2.3/100,000 with a slightly higher rate of occurrence in men than in women (1.2:1).[1] The median age of diagnosis is 60 years. Polycythemia can be either relative polycythemia or true polycythemia. Relative polycythemia occurs due to a reduction in plasma volume (e.g.: diuretic use, severe burns, vomiting, diarrhea, severe dehydration, etc.). True polycythemia can be either primary or secondary. Primary polycythemia is one of the chronic myeloproliferative disorders called as polycythemia vera. Secondary polycythemia is due to excess erythropoietin production in case of hypoxia, malignant conditions (hepatocellular cancer, renal cell cancer, cerebellar hemangioblastoma, and parathyroid carcinoma), uterine leiomyoma, renal cyst, and meningioma.[1]

The symptoms of PV include pruritus (especially after hot shower), headache, paresthesia, dizziness, visual disturbance, bleeding, and peptic ulcer disease.[2] The vascular complications in PV due to increased blood viscosity are microvascular circulatory disturbances typical of thrombocythemia including erythromelalgia, peripheral ischemia, myocardial infarction, atypical cerebral ischemic attacks, and major arterial and venous thrombotic events.[3] The life-threatening complications include cardiovascular complications and progression to post-PV myelofibrosis or leukemia. Approximately 12—21% of patients with PV develop post-PV myelofibrosis, and approximately 7% develop leukemia within 20 years.[4] Polycythemia should be suspected when there is an elevated level of hemoglobin or hematocrit on normal oxygen saturation. However, as in the case discussed above, the finding can be masked in severe anemia. Other common findings also include an elevated white blood cell count, thrombocytosis, elevated lactate dehydrogenase, and splenomegaly. Serum erythropoietin is to be evaluated to differentiate between primary and secondary polycythemia. Low erythropoietin is suggestive of PV, which can be confirmed with a positive JAK2 mutation. The JAK2V617F mutation is positive for around 95% of patients; a further 2—4% of patients harbor mutations in JAK2 exon 12.[5] Patients with low erythropoietin and negative JAK2V617F should be screened for JAK2 exon 12 mutation. Bone marrow biopsy reveals hypercellularity, an increased number of megakaryocytes, giant megakaryocytes with pleomorphism in megakaryocyte morphology, mild reticulin fibrosis (in 12% of patients), and decreased bone marrow iron stores.[1] The World Health Organization diagnostic criteria for PV include two major and three minor criteria. The first major criterion is Hb >18.5 g/dL in men and 16.5 g/dL in women, or evidence of increased red cell volume (like increased hematocrit >99th percentile of method-specific reference range for age, sex, and altitude of residence). The second major criterion is a positive JAK2V617F mutation or presence of functionally similar mutations such as JAK2 exon 12 mutations. The minor criteria include serum erythropoietin below the normal reference range; bone marrow biopsy showing hypercellularity for age with trilineage growth with prominent erythroid, granulocyte, and megakaryocyte proliferation; and endogenous erythroid colony formation in vitro. The diagnosis of PV requires the presence of two major criteria plus one minor

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criterion, or the presence of the first major criterion plus two minor criteria.

Since there is no proven drug that aims to completely cure PV, the treatment is mainly focused on preventing thrombotic events and its progression to PV myelofibrosis and leukemia without increasing bleeding tendency. The mainstay of treatment is phlebotomy, to keep the hematocrit level below 45%. Initially, chlorambucil, pipobroman, and radioactive phosphorus were used to treat PV; however, pipobroman and radioactive phosphorus were known to increase the incidence of acute leukemia.[6,7] Among the cytoreductive agents, hydroxyurea is the first line of drug recommended for controlling the proliferative phase of PV. It is well tolerated and least toxic as compared with the second-line drugs that include ruxolitinib, interferon, and busulfan. In one of the trials, patients treated with ruxolitinib, which is a Janus kinase 1/Janus kinase 2 inhibitor, were found to have good hematocrit control without phlebotomy and a decrease in spleen size.[8] Interferon alpha mainly acts by decreasing JAK2V617F mutation allele and also helps in controlling severe pruritus, but the major drawback is that it is highly toxic. Busulfan is reserved for patients who do not respond to hydroxyurea due to its potential side effects. The patients who fail to respond to hydroxyurea have a 5.6-fold increase in mortality and a 6.8-fold increase in the risk of transformation to myelofibrosis or acute myeloid leukemia, and hence second-line drugs are preferred despite their side effects.[9] Low-dose aspirin is recommended for prevention of thrombotic events if there is no contraindication. Antihistamines are used to treat pruritus. In a study, iron supplementation was recommended to treat pruritus for patients who had iron deficiency in PV.[10] Indiscriminate usage of iron is not recommended, as it would progressively increase the red cell mass. Apart from symptomatic management of PV, other measures to prevent thrombosis and bleeding are to treat existing conditions such as hypertension, diabetes, hyperlipidemia, and hypercholesterolemia; avoid oral contraception and smoking; adopt healthy lifestyle modifications. The median survival of treated patients is 13 years or more and that of untreated patients ranges between 6 months and 18 months from diagnosis.[11] However, factors such as age >70 years, white blood count >13 k/μL, and thromboembolism at the time of diagnosis were considered as independent risk factors for survival.[12]

Very few patients present with actual symptoms, and most are diagnosed on routine laboratory investigation. In our patient, the diagnosis was masked due to severe anemia in the past, although she had elevated white cell and platelet counts in the past. Her hemoglobin level started increasing only after she became amenorrheic and was placed on iron replacement. An early diagnosis could have been possible if her elevated white cell count was considered as a differential diagnosis of a myeloproliferative disorder after ruling out infection with negative culture.

Conflicts of interest

None.

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